

Applicant : Shawn Shui-On Leung
U.S. Serial No.: 09/892,613
Filed : June 27, 2001
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Amendments to the specification:

Application title

Applicant requests the amendment of the originally filed title of the application by inserting the underlined text and deleting the strikethrough text as follows:

~~"REDUCING IMMUNOGENICITIES OF IMMUNOGLOBULINS BY FRAMEWORK-PATCHED IMMUNOGLOBULINS"~~

Pages 7-8, Detailed description of the Figures

Applicant requests the amendment of the detailed description of Figures 1-3 and 7-10 by inserting the underlined texts.

Fig. 1A and Fig. 1B. Amino acid sequences (single-letter code) of the heavy chain (VH) (A) and light chain (VL) (B) variable regions of the murine anti-CD22 antibody, RFB4. CDR's are boxed.
(SEQ ID NO. 33 AND 34)

Fig. 2A and Fig. 2B. Comparison of the compartmentalized framework sequences (FR's) of the heavy chain (A) and light chain (B) variable regions of RFB4, with the different human FR's of the highest homology. The FR1, FR2, FR3, and FR4 are indicated. The CDR's are boxed. The bracketed italic next on the left of the FR sequence indicates the source of the human FR. Amino acids in the human FR's that are different from that of the corresponding murine FR's are in bold. (SEQ ID NO. 35-46)

Fig. 3A and Fig. 3B. The final designed sequences (single-letter

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code) of the heavy chain (A) and light chain (B) variable regions of the FR-patched antibody, hpRFB4. CDR's are boxed. Amino acids in the human FR's that are different from that of the original murine FR's are in bold. (SEQ ID NO. 47-48)

Fig. 7A and Fig. 7B. Amino acid sequences (single-letter code) of the heavy chain (A) and light chain (B) variable regions of the murine anti-CD20 antibody, 1F5. CDR's are boxed. (SEQ ID NO. 49-50)

Fig. 8A and Fig. 8B. Comparison of the compartmentalized framework sequences (FR's) of the heavy chain (A) and light chain (B) variable regions of 1F5 with the different human FR's of the highest homology. The FR1, FR2, FR3, and FR4 are indicated. The CDR's are boxed. The bracketed italic next on the left of the FR sequence indicates the source of the human FR. Amino acids in the human FR's that are different from that of the corresponding murine FR's are in bold. (SEQ ID NO. 51-67)

Fig. 9A and Fig. 9B. The final designed sequences (single-letter code) of the heavy chain (A) and light chain (B) variable regions of the FR-patched antibody, hp1F5. CDR's are boxed. Amino acids in the human FR's that are different from that of the original murine FR's are in bold. Murine FR's not replaced by human sequences are underlined. (SEQ ID NO. 68-69)

Fig. 10. Amino acid sequence of an alternative design of FR-patched variable regions for 1F5 (Alternative Design). CDR's are boxed. Human framework amino acids that differ from that of the corresponding murine frameworks are in bold. A. The heavy chain

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variable region (VH) amino acid sequence of FR-patched 1F5
(Alternative Design); (SEQ ID NO. 70) B. The light chain
variable region (VL) amino acid sequence of FR-patched 1F5
(Alternative Design). (SEQ ID NO. 71)

Page 11, second full paragraph

Applicant requests replacement of the paragraph with the following paragraph, inserting the underlined text and deleting the strikethrough text.

Chimeric antibodies are antibodies whose variable regions are linked, without significant sequence modifications from the parent V-region sequences, to the corresponding heavy and light chain constant regions of a different species. Construction of a chimeric antibody is usually accomplished by ligating the DNA sequences encoding the variable regions to the DNA sequences encoding the corresponding constant chains. The most common types of chimeric antibodies are those containing murine variable regions and human constant regions. In this case, the expressed hybrid molecule will have the binding specificity and affinity of the parent murine antibody, and the effector functions of a human antibody. Most importantly, 2/3 of the amino acids of the recombinant protein are of human origin, a reduced or insignificant immunogenicity is therefore expected when used in human, as in the case of the therapeutic chimeric antibody C2B8 (or Rituxan Rituximab) (Davis et al., J. Clin. Oncol. 17:1851-1857, 1999; Coiffier et al., Blood 92:1927-1932, 1998; McLaughlin et al., J. Clin. Oncol. 16:2825-2833, 1998).